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# Relationship of Vitamin B12 Level in Breastfeeding Mothers with Vitamin B12 and Homocysteine Levels of Infants

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**What is known on this subject?**

The vitamin B12 and homocysteine levels of breastfed infants were investigated. It was shown that these results were affected by the mother's vitamin B12 level. It was investigated what the mother's vitamin B12 level should be for infants to be healthier.

**What this study adds?**

It has been shown that maternal vitamin B12 levels affect infant B12 and homocystin levels. It has been shown that B12 deficiency is very common in mothers, and B12 deficiency and elevated homocysteine are very common in infants.

## ABSTRACT

**Objective:** Vitamin B12 deficiency, an essential vitamin for the human body, is common in Turkey, and infants are at risk in this regard. This study was intended to investigate the effect of vitamin B12 levels of breastfeeding mothers with infant vitamin B12 and homocysteine levels.

**Material and Methods:** A total of 214 infants aged 1-6 months and their mothers who applied to the infancy outpatient clinic of İstanbul Medeniyet University Göztepe Training and Research Hospital were included in the study. In this study, vitamin B12 levels of the mothers, vitamin B12, folic acid, and homocysteine levels in the infants were primarily analyzed, and the associated risk factors were secondarily determined.

**Results:** The rate of adequate vitamin B12 levels in infants was 20.09% (n=43), and the rate of normal homocysteine levels in mothers of infants with sufficient vitamin B12 and normal homocysteine levels was 383.93 pg/mL and 379.07 pg/mL. 66.27% sensitivity and 75.56% specificity were calculated when 220 pg/mL was taken as the vitamin B12 cut-off value, which predicts homocysteine elevation.

**Conclusion:** This study predicted that only one in five infants had sufficient vitamin B12 levels, but if breastfeeding mothers had sufficient vitamin B12 levels, infants were much less likely to have vitamin B12 deficiency. Since adequate vitamin B12 levels are important for infants, especially in terms of neurodevelopment, we believe that it is necessary to evaluate pregnant women in our society in terms of vitamin B12 levels and to provide vitamin B12 support.

**Keywords:** Vitamin B12, homocysteine, pregnant, infant, lactation

## Introduction

Vitamin B12, which is obtained from animal foods, is an essential vitamin for humans, and since it cannot be synthesized in the human body, it should be taken regularly in the diet. An adult human liver has an average of 2000 mcg of vitamin B12 storage, whereas a newborn's liver has 25-30 mcg of vitamin B12 storage (1). It has been shown that infants of pregnant women with low vitamin B12 levels do not have sufficient vitamin B12 levels (2).

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Vitamin B12 is involved in important reactions in the body, especially in cell division (3,4,5,6).

In a few studies conducted in Turkey, vitamin B12 deficiency in the neonatal period was found to be 42% (7) and 74.2% (8), and this deficiency rate was 73% (9) in the geriatric age group, and data on the pediatric age group were insufficient. In Turkey, where vitamin B12 deficiency is common, infants who do not receive the necessary vitamin B12 support from their mother during the fetal period are expected to be born with low vitamin B12 storage. Therefore, pregnant women and mothers should have an extra well-being for their infants in addition to their own health. According to the recommendation of the United States National Institute of Health, the daily cobalamin requirement is 0.4 mg/day in early infancy, 2.4 mg/day in adulthood, and these requirements slightly increase during lactation and pregnancy. These recommendations are 2.6 mcg/day during pregnancy and 2.8 mcg/day during lactation (1,10). The World Health Organization routinely recommends iron and flaccid supplementation in pregnant women, but there is no routine recommendation for vitamin B12 supplementation (11).

Vitamin B12 deficiency can be clinically asymptomatic and can present as signs in many systems, especially hematological and neurological symptoms (12). Megaloblastic anemia, delayed neurological development in infants, delayed myelination and hypotonia, and peripheral sensory neuropathy are common signs (13,14).

Breastmilk is the only food source for infants in the first six months of life, and all micro- and macronutrients are transferred to the infant through breastmilk. It has been shown in studies that the mother's vitamin B12 level correlates with the vitamin B12 level in breastmilk and infant serum (6,7,8). In addition, there is a study showing that vitamin B12 and folic acid levels in pregnancy affect the homocysteine level of the infant at 2 years old. However, considering that infants up to the age of two will be severely affected by mixed nutrition, it should not be considered that the vitamin B12 and folic acids of the infants in this study should be affected only by the condition in pregnancy (15). Additionally, studies conducted in Turkey have been based on the relationship between pregnant women and newborn infants and have been conducted with working groups that are under the influence of fetal life (7,8), but there have been no studies on infants in the lactation period. In addition to detecting the vitamin B12 relationship between mothers and infants during lactation, one of the objectives of this study was to reveal the optimal vitamin B12 value for infants. The primary motivation of our study was that no study determining the optimal vitamin B12 level in infants was found in the literature at the time of the study.

Based on this information, this study aimed to determine the relationship between vitamin B12 levels in breastfeeding mothers and vitamin B12 and homocysteine levels in infants and the ideal vitamin B12 level of infants at 1-6 months of age and to determine the associated risk factors.

## Material and Methods

This retrospective study was conducted between November 01, 2018 and November 21, 2019 at University of Health Sciences Turkey, İstanbul Medeniyet University Göztepe Training and Research Hospital by collecting data from 1-6-month-old infants with vitamin B12 and homocysteine values and their mothers whose vitamin B12 values were measured within 15 days. Infants who had a normal birth time and weight (>37 GW, >2500 gr), did not use vitamin B12 and folic acid, did not take formula or supplements, and donated human milk, did not have any additional disease (congenital heart disease, neurodevelopment retardation, chronical systemic disease, chronical respiratuar failure, metabolic disease, chronical renal disease, malnutrition, malabsorption) or clinical infections, and mothers who did not have malnutrition, intestinal malabsorption, or clinical infection, did not use metformin or proton pump inhibitors, had not undergone metabolic surgery, and did not use drugs containing vitamin B12 at that time were included in the study.

Study groups were formed with 214 infants and their mothers who met the inclusion criteria.

Mothers' vitamin B12 levels and infants' vitamin B12 and homocysteine levels simultaneously were compared, and their relationship was examined. Vitamin B12 level was defined as deficiency below 200 pg/mL, insufficiency in the range of 200-300 pg/mL, and adequacy above 300 pg/mL (12,16), while folic acid reference values below 3 ng/mL were defined as insufficiency, 3-5 ng/mL deficiency, 5-20 ng/mL adequacy (17). For infants, the age-appropriate homocysteine reference value of 3.3-8.3 µmol/L was defined as normal (18,19). The correlation of vitamin B12 level with birth weight, postnatal age at which the vitamin B12 test was performed, and whether mothers used vitamin B12 at the daily required dose (2.5-3 mcg) in the last 3 months of pregnancy were examined.

Prior to study commencement, permission was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Medeniyet University Göztepe Training and Research Hospital (decision no: 2019/0523, date: 25.12.2019).

### Statistical Analysis

Statistical analysis was performed with the help of SPSS version 17.0. The normality of the variables to the normal distribution was examined using dusing histogram graphics and Kolmogorov-Smirnov test. Mean, standard deviation, and median values were used while presenting descriptive analysis. The Mann-Whitney U test was used to evaluate values that did not show normal distribution (non-parametric) between two groups, and the Kruskal-Wallis test was used to evaluate values between more than two groups. The Spearman correlation test was used to analyze the measurable data according to one another. Receiver operating characteristic curve analysis was used to find a cut-off value for vitamin B12 in infants that can predict high homocysteine levels. Cases with a p value 0.05 were considered statistically significant.

## Results

Two hundred and fourteen infants were included in the study. 45.33% (n=97) of the infants were born with normal spontaneous vaginal delivery, and 54.67% (n=117) were born with cesarean section. It was detected that the B12 deficiency in 50.47% (n=108) of infants, B12 insufficiency in 29.44% (n=63) of infants, B12 deficiency in 14.95% (n=32) of mothers, B12 insufficiency in 31.78% (n=68) of mothers. Homocysteine elevation was found in 78.97% (n=169) of infants, whereas the folate value was 100% (n=122) of infants whose folate was measured as normal (Table 1).

The correlation between maternal vitamin B12 levels and infant vitamin B12, infant homocysteine, and the number of meals consumed in meat per week was analyzed. Accordingly, a statistically significant positive correlation was observed between maternal vitamin B12 level and infant B12 level; there was a significant negative correlation between maternal vitamin B12 level and infant homocysteine level ($p<0.001$, Table 2). No significant correlation was found between the vitamin B12 level of mother and the number of meals consumed in meat weekly ($p=0.475$, Table 2).

The rate of vitamin B12 supplementation in the last 3 months of pregnancy was 72.43% (n=155) (Table 1). Compared with the B12 and homocysteine levels of the infants of mothers who used B12-containing vitamins for the last 3 months during pregnancy and the infants whose mothers did not use it; the vitamin B12 levels of the infants of mothers who used vitamin B12-containing vitamins in the last 3 months of pregnancy were statistically significantly higher than the others ($p=0.003$, Table 3). However, no significant relationship was found between the homocysteine levels of infants whose mothers used B12-containing vitamins for the last 3 months during pregnancy and those who did not ($p=0.063$, Table 3).

The study also examined the correlation between birth weight and B12 levels of infants, but no significant relationship was found ($p=0.412$, data is not shown). According to postnatal age, there was also no significant relationship between

**Table 1. Demographic characteristics and vitamin levels of the study groups**

| Parameters | | n | % |
|---|---|---|---|
| Postnatal age (days) | 30-60 days | 80 | 37.38 |
| | 61-120 days | 93 | 43.46 |
| | 121-180 days | 41 | 19.16 |
| Form of delivery | Vaginal | 97 | 45.33 |
| | C/S | 117 | 54.67 |
| B12 supplementation during the last 3 months after birth | Yes | 155 | 72.43 |
| | No | 59 | 27.57 |
| Mothers' vitamin B12 level status | Deficiency | 32 | 14.95 |
| | Insufficiency | 68 | 31.78 |
| | Adequacy | 114 | 53.27 |
| Infant vitamin B12 level status | Deficiency | 108 | 50.47 |
| | Insufficiency | 63 | 29.44 |
| | Adequacy | 43 | 20.09 |
| Infant homocysteine level status | Normal | 45 | 21.03 |
| | High | 169 | 78.97 |
| Infant folic acid level status | Normal | 122 | 100.00 |

*C/S: Cesarean section*

**Table 2.** Correlation between maternal vitamin B12 level and maternal age

| Parameters | | Mothers' vitamin B12 |
|---|---|---|
| **Infants' vitamin B12 levels** | R | 0.372 |
| | P | <0.001 |
| **Infants' homocysteine** | R | -0.376 |
| | P | <0.001 |
| **Amount of meat meals the mother consumes per week** | R | 0.049 |
| | P | 0.475 |

*Spearman correlation test*

**Table 3.** Effect of using B12 vitamin in pregnancy on infants'

| | B12 supplementation during the last 3 months after birth | | p |
|---|---|---|---|
| | Yes | No | |
| *Infants' vitamin B12 level (pg/mL) | 247.43±131.81 | 193.24±89.73 | 0.003 |
| *Infants' homocysteine level (mcd/dL) | 12.08±5.30 | 13.89±6.55 | 0.063 |

*Mann-Whitney U test, *Mean ± SD*
*SD: Standard deviation*

vitamin B12 level was compared between infant and mother (data is not shown).

Mother's vitamin B12 levels were examined according to the infants with vitamin B12 >300 pg/mL and normal homocysteine level. Mothers with infants with vitamin B12 levels >300 pg/mL were found to be significantly higher than those without vitamin B12 value (p<0.001, Table 4). Similarly, mothers with normal infant homocysteine levels were significantly more likely to have high vitamin B12 levels than those with high vitamin B12 levels (p<0.001 Table 4).

Infants with normal homocysteine had an average vitamin B12 level of 301.31±119.01 pg/mL, whereas infants with high homocysteine had 214.16±118.90 pg/mL, and there was a statistically significant difference between them (p<0.001, data is not shown).

The presence of a cut-off value was examined using receiver operating characteristic analysis of the vitamin B12 level to predict the normal level of homocysteine. When determining this value, it was noted that the percentage of both sensitivity and specificity was high, and 220 pg/L was selected as the value that met the criteria. According to this, 66.27% sensitivity, 75.56% specificity, 91.06% positive predictive value, and 37.36% negative predictive value were calculated when the cut-off value was 220 pg/mL (Figure 1, table data is not shown).

When mothers' vitamin B12 levels were examined as groups; vitamin B12 levels of infants with maternal B12 levels >385 pg/mL were higher than those with maternal B12 levels between 300-384 pg/mL and those with <300 pg/mL (p<0.001, Table 5). The homocysteine levels of infants with maternal B12 levels >385 pg/mL were lower than those with maternal B12 levels between 300-384 pg/mL and those with <300 pg/mL (p<0.001, Table 5).

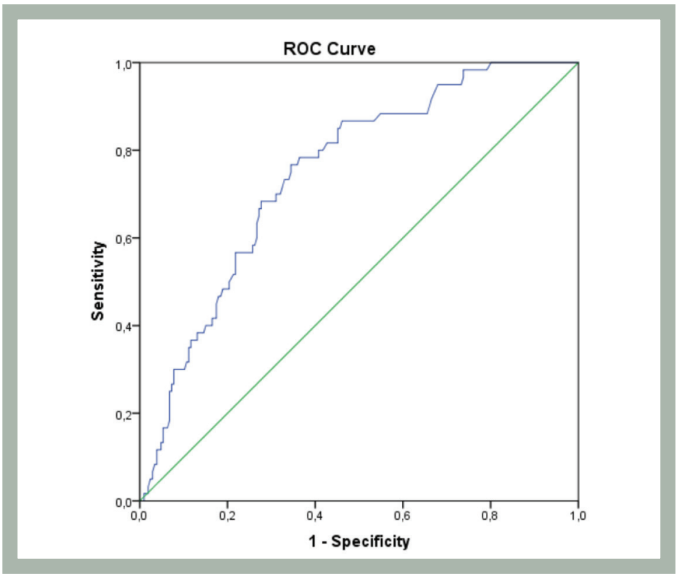


**Figure 1.** Receiver operating characteristic analysis of vitamin B12 value to predict the normal homocysteine level

*ROC: Receiver operating characteristic*

**Table 4.** Mothers' vitamin B12 levels according to the B12 vitamin and homocysteine status of infants

| Parameters | | Mothers' B12 vitamin level | p |
|---|---|---|---|
| *Infants' B12 vitamin level (pg/mL) | <300 | 300.25±104.48 | <0.001 |
| | >300 | 383.93±135.90 | |
| *Infants' homocysteine level (mcg/dL) | Normal | 379.07±123.89 | <0.001 |
| | High | 300.55±108.50 | |

*Mann-Whitney U test, *Mean ± SD*
*SD: Standard deviation*

**Table 5.** Infant B12 vitamin and homocysteine levels according to the mother's vitamin B12 level

| | Mothers' B12 vitamin level (pg/mL) | | | |
|---|---|---|---|---|
| | <300 | 300-385 | >385 | p |
| | Mean ± SD | Mean ± SD | Mean ± SD | |
| Infant B12 vitamin level (pg/mL) | 196.01±110.28 | 236.03±113.04 | 293.95±134.20 | <0.001 |
| *Infants' homocysteine level (mcg/dL) | 14.41±6.54 | 12.06±4.72 | 9.86±3.55 | <0.001 |

**Kruskal-Wallis test, SD: Standard deviation*

## Discussion

When the results of 214 infants and their mothers were evaluated in our study, the rate of infants with vitamin B12 levels below 200 pg/mL was 50.4%, and the rate of infants with vitamin B12 levels of 200-300 pg/mL, which is known as insufficient, was 29.4%. When the set two results were evaluated together, the rate of infants with a vitamin B12 value below 300 pg/mL was found to be 79.8%, and this value is higher than 61%, which was determined by Yetim et al. (20) from cord blood in the neonatal period. However, it could not be compared because there were no studies conducted on infants in Turkey.

It has been proven that there is a strong correlation between serum vitamin B12 levels in pregnant women and vitamin B12 levels in cord blood. In a study of Yetim et al. (20) on newborns' cord blood, vitamin B12 levels were found below 300 pg/mL in 93% of pregnant women's serum and 61% of cord blood, and folic acid deficiency was not detected in any of the mothers or infants. Folic acid deficiency, which is another cause of homocysteine height, was not detected in any of the 122 infants whose folic acid levels were measured in our study. This result proves that the homocysteine elevation in our patients was caused by vitamin B12 deficiency. The most important reason for the absence of folic acid deficiency was the use of 400 g of folic acid support given during pregnancy except 8 patients. Although the vitamin B12 level of newborns in the proposal study was 42%, with a rate of infants with a level below 200 pg/mL, in our study, 50.4% was found in infants who are 1-6 months of age, and although the differences in the study groups were considered, infants experienced severe vitamin B12 deficiency from the neonatal period (7). Önal et al. (7) also stated in this study that the vitamin B12 level of infants decreased after the postnatal 15$^{th}$ day; in our study, infants in the 1-6 month period had more vitamin B12 deficiency than in the newborn period, but in our study, no significant differences were found between them selves when infants aged 1-6 months were divided into 3 age groups.

According to the data obtained in our study, the vitamin B12 level was 200 pg/mL in 14.9% of breastfeeding mothers, and the rate of mothers with sufficient B12 vitamin levels at 200-300 pg/mL was 31.7%. According to the statistics, vitamin B12 deficiency, which is common in our society, was significantly higher in breastfeeding mothers, and the vitamin B12 level of infants fed by these mothers was also low in correlation with the mother (Table 2).

When the relationship between vitamin B12 obtained from animal foods and the nutrition of the mother was examined, a limited history was taken regarding how many meals of meat they consumed weekly, as the nutritional anamnesis of the mothers could not be assessed in detail, and this anamnesis was not significantly associated with her vitamin B12 level ($p>0.05$). The probable cause of this situation was the incomplete declaration of the families.

In our study, it was found that mother's vitamin B12 level and infants' vitamin B12 level showed a positive correlation, whereas the infants' homocysteine level showed a negative correlation, as expected. In a study by Siddiqua et al. (21) in Bangladesh, a negative correlation was found between maternal vitamin B12 levels and infant homocysteine level,

however, no studies involving homocysteine levels were found in Turkey or other European countries. A retrospective study conducted by Akcaboy et al. (22) in Turkey in 2014 on infants with vitamin B12 deficiency found vitamin B12 deficiency in all their mothers.

In addition, we found that the average vitamin B12 level of infants whose mothers used supplements containing vitamin B12 in the last 3 months of pregnancy was significantly higher than that of infants who did not use it (p=0.003, Table 3). It was found that a difference of 54 pg/mL occurred when the values of the two groups of infants were compared. For this reason, we believe that it is important that pregnant women are evaluated for vitamin B12 levels when initiating iron and folic acid replacement during their follow-up programs.

In another study, a multicenter study conducted by Chebaya et al. (6) examined the relationship between maternal serum, breastmilk, and infant serum B12 levels in Canadian and Cambodians during lactation. It was reported that Canadian mothers took vitamin B12 supplements during pregnancy and lactation, but Cambodian mothers did not, and the vitamin B12 levels of Canadian mothers were found to be statistically significantly higher due to their better socio-economic status and their use of vitamin B12 supplements. In Canada, maternal serum, breast milk, and infant serum vitamin B12 levels were significantly correlated, and in Cambodian mothers, a correlation was found between maternal and infant serum vitamin B12 levels. Vitamin supplement use has positive effects on infant and mother's vitamin B12 values, but mother and infant B12 vitamin levels are directly related regardless of supplement use. In our study, a strong correlation between maternal and infant vitamin B12 levels was observed, which supports this study.

In our study, infants were divided into 3 groups as 31-60 days old, 61-120 days old, 121-180 days old according to postnatal age after the neonatal period, and no significant differences were found between age groups when values in terms of vitamin B12 levels were taken. In the study conducted on Cambodian and Canadian mothers, infants were divided into two groups according to postnatal age, as before and after 8 weeks of pregnancy, and it was shown that they had lower vitamin B12 levels as postnatal age progressed, but no statistically significant difference was found (6). Compared with studies on vitamin B12 deficiency during the neonatal period in Turkey (7,8,20). Infants in our study had a higher rate of vitamin B12 deficiency, which supports the study conducted by Chebaya et al. (6) from Canada. Although the level of vitamin B12 decreases in 1-6 months period, there is no statistically significant difference (Table 4).

A statistically significant difference was found between the vitamin B12 levels of the mothers when the infants had adequate vitamin B12 and normal homocysteine levels compared with those who did not. In this study, it should be considered that the vitamin B12 level of mothers should be kept above 385 pg/mL in order for infants to have sufficient vitamin B12 and normal homocysteine levels. For mothers, this review was first introduced in our study.

In the adult age group, the normal vitamin B12 level is 300 pg/mL, and insufficiency is indicated as 200-300 pg/mL (16). A 90% sensitivity to normal vitamin B12 levels has been reported. Currently, we know that a level of 300 pg/mL does not show 100% sensitivity, and according to the results of our study, we believe that a level of 300 pg/mL of vitamin B12 in mothers is insufficient for infants fed to breastfeeding mothers. It is one of the results of our study that if breastfeeding mother's vitamin B12 level can be maintained above 385 pg/mL, the infant can have vitamin B12 levels above 300 pg/mL and homocysteine levels below 8.3 µmol/L.

Clinical findings of vitamin B12 deficiency were not evaluated in our study, in a study by Lai et al. (23); when the cognitive scores of 2-year-old children of pregnant women who were followed up in 2 groups as those with and without vitamin B12 deficiency during pregnancy were compared, the cognitive score of the group with vitamin B12 deficiency was found to be significantly lower. But in this study, while the presence of many environmental, familial, and genetic factors that can affect the cognitive functions of infants restricts reliability, vitamin B12 deficiency can also be considered as a risk factor for neurodevelopmental retardation.

The effects of persistent hyperhomocysteinemia on cerebrovascular events, diabetes development, and cardiovascular events in adults are known (24,25). Vitamin B12 deficiency in infancy, childhood, and old age is one of the leading causes of hyperhomocysteinemia (18). One of the most common causes of vitamin B12 deficiency in the infant group is low vitamin B12 storage and insufficient intake due to maternal vitamin B12 deficiency (26).

In Turkey, there are valuable studies on pregnant women and newborns regarding vitamin B12 levels, but there is not enough data on the relationship between vitamin B12 and homocysteine levels during the infant period (6,9).

In our study, the cut-off vitamin B12 level was found for the first time in order to predict the elevation of homocysteine in the infant period and was found to be 220 pg/mL, and the values detected for 220 pg/mL are as indicated: sensitivity, 66.2%; specificity, 75.5%; negative predictive value: 37.3%; and positive predictive value, 91.0%. Accordingly, the homocysteine

elevation rate of those with vitamin B12 levels below 220 pg/mL was 91%, whereas the homocysteine normality rate of those above 220 pg/mL was 37.3%. The reason for this is that a majority of our infant patients had vitamin B12 levels below 300 pg/mL. We can say that the average vitamin B12 level of infants with normal homocysteine levels is 301.3 pg/mL and that is the normal cut-off value of 300 pg/mL and its above can also be used as a safe range for infants.

In a study conducted in Turkey, the B12 vitamin cut-off value of newborns was 232.5 pg/mL with 70% specificity and sensitivity, and the homocysteine value of 4.7 µmol/L was determined as the cut-off value for 58% specificity and 68% sensitivity (20). It has been shown in these two studies that infant and neonatal homocysteine levels are significantly lower than adult homocysteine levels.

## Conclusion

In addition, as detected in our study, vitamin B12 deficiency is common among infants and breastfeeding mothers. Since vitamin B12 deficiency is common in developing countries such as Turkey, infants can be protected from vitamin B12 deficiency, especially by preventing mothers' vitamin B12 deficiency. Our recommendation is to check the vitamin B12 level in the early period of pregnancy follow-up, since vitamin B12 deficiency is very common in Turkey, to start daily maintenance B12 at a dose of 2-5 mcg if there is a deficiency, to start preparations containing vitamin B12 in a maintenance dose, and continue during lactation. In this way, fetal vitamin B12 stores can be sufficiently formed during pregnancy, and during lactation, infants can receive sufficient levels of maintenance B12 vitamins through the mother.

### Ethics

**Ethics Committee Approval:** Ethical approval was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Medeniyet University Göztepe Training and Research Hospital (decision no: 2019/0523, date: 25.12.2019).

**Informed Consent:** Retrospective study.

### Authorship Contributions

Surgical and Medical Practices: S.P., Concept: S.P., Design: S.P., Data Collection or Processing: S.P., Analysis or Interpretation: S.P., A.K., Literature Search: S.P., A.K., Writing: S.P.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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